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Notices

DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)

Public Health Service (PHS)

Food and Drug Administration (FDA)

[Docket No. 93N-0238]

Intent to Conduct a Comprehensive Toxicological Assessment of Chloral Hydrate

58 FR 39558

DATE: Friday, July 23, 1993

ACTION: Notice.

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SUMMARY: The Food and Drug Administration (FDA) is announcing that it intends to conduct a comprehensive toxicological assessment of chloral hydrate. This study will be conducted under an interagency agreement between FDA and the National Institute of Environmental Health Sciences (NIEHS), whereby FDA will conduct comprehensive toxicological assessments on certain chemicals or agents in the **National Toxicology Program** (NTP). FDA invites interested parties to submit relevant information, including ongoing toxicological studies, current or future trends in use patterns and human exposure levels, and toxicological data.

DATES: Written information by August 23, 1993.

ADDRESSES: Submit written information to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William T. Allaben, National Center for Toxicological Research (HFT-30), Food and Drug Administration, 3900 NCTR Rd., Jefferson, AR 72079-9502, 501-543-7211.

SUPPLEMENTARY INFORMATION: In December 1992, FDA's National Center for Toxicological Research (NCTR) and NIEHS entered into an agreement whereby NCTR would conduct comprehensive toxicological assessments on selected chemicals. These toxicological assessments would be part of the NTP and would be designed to facilitate the interpretation of study results in support of comprehensive human health risk assessments. The program is intended to develop a comprehensive scientific data base that can be utilized to reduce the uncertainty in risk assessment/risk benefit analysis for specific chemicals.

As a member agency in the NTP, FDA has the opportunity to nominate one chemical annually for testing consideration. This nomination process is conducted by FDA's chemical selection working group. With this notice, FDA is announcing its intent to conduct a comprehensive toxicological assessment of chloral hydrate.

Chloral hydrate (2,2,2-Trichloro-1,1-ethanediol; CAS Reg. No. 302-17-0; Csub 2Hsub 3Clsub 3Osub 2) was first synthesized in 1832 and was introduced as a hypnotic drug in 1869. It continues to be used today as a sedative/hypnotic, primarily for children and elderly patients (Ref. 1). It is used as a sedative administered to children in dental procedures (Ref. 2) and in ophthalmoscopic procedures (Ref. 1). Additionally, chloral hydrate is commonly used to sedate neonates to decrease agitation when they are undergoing mechanical ventilation (Ref. 3) or to assure quiescence during imaging procedures (Ref. 4). Dosages in children range up to 60 milligrams (mg) per kilogram, whereas adult dosages range from 250 mg when used as a sedative, to 500 to 1,000 mg when used as a hypnotic.

In veterinary medicine, chloral hydrate is used as a central nervous system depressant, as a sedative, and for general anesthesia in cattle and horses.

In a recent screening study conducted by the Environmental Protection Agency, chloral hydrate was indicated as a possible male mouse liver tumorigen (Ref. 5). It has also been reported to be mutagenic or genotoxic in some prokaryotic and eukaryotic assay systems (Refs. 6 through 13). Other screening studies suggest that one major metabolite of chloral hydrate, trichloroacetic acid, may also be a male mouse tumorigen, and trichloroethylene (TRI) and perchloroethylene, both of which may be metabolized to chloral hydrate in rodents, have been shown to be carcinogenic in mice or rats (Refs. 14 through 17). Additionally, TRI and a major metabolite of chloral hydrate, trichloroethanol, have been reported to be mutagenic or genotoxic in some assay systems (Ref. 18).

While FDA is aware of some studies suggesting that chloral hydrate may be toxic in some animal models, there is no epidemiological evidence to suggest it presents a health risk to humans. Nevertheless, the agency believes there is a need to do a comprehensive toxicological assessment of chloral hydrate. This comprehensive toxicological assessment may include animal metabolite/pharmacokinetic studies for comparison to known (or planned) human pharmacokinetic studies in adults and children; range-finding studies; subchronic and chronic studies in appropriate animal models, including a dose-stop study; toxicokinetic studies; mutagenic evaluation using human cell lines expressing specific cytochrome P-450 isozymes; evaluation for and identification of specific deoxyribonucleic acid adducts; determination of cellular and peroxisome proliferation; modulation by dietary restrictions of activating/detoxifying chloral hydrate metabolic pathways in animal models; and an assessment of neurotoxicity.

References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Blacow, N. W., editor, *Martindale: The Extra Pharmacopeia*, 26th ed., London, the Pharmaceutical Press, 898-900, 1973.
2. Smith, M. T., "Chloral Hydrate Warning," *Science*, p. 359, October 19, 1990.
3. Gorecki, D. K. J., et al., "Determination of Chloral Hydrate Metabolism in Adult and Neonate Biological Fluids After Single-Dose Administration," *Journal of Chromatography*, 528:333-341, 1990.
4. Neuman, G., L. Kushins, and S. Ferrante, "Sedation for Children Undergoing Magnetic Resonance Imaging and Computerized Tomography," *Anesthesia and Analgesia*, 74:931-932, 1990.
5. Daniel, F.B., et al., "Hepatocarcinogenicity of Chloral Hydrate, 2-Chloroacetaldehyde, and Dichloroacetic Acid in the Male B6C3F1 Mouse," *Fundamental and Applied Toxicology*, 19:159-168, 1992.

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7. Carere, A., et al., "In Vitro and In Vivo Genotoxic Effects of Trichloroethylene and its Metabolites," *Mutation Research*, 130:247, 1984.
8. Parry, J. M. and S. James, "The Detection of Aneugenic Chemicals Using Yeast Strain D6," *Mutagenesis*, 3:447, 1988.
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10. Waskell, L., "A Study of the Mutagenicity of Anesthetics and Their Metabolites," *Mutation Research*, 57:141-153, 1978.
11. Bignami, M., et al., "Mutagenicity of Halogenated Aliphatic Hydrocarbons in *Salmonella typhimurium*, *Streptomyces coelicolor*, and *Aspergillus nidulans*," *Chemical and Biological Interactions*, 30:9-23, 1980.
12. Nelson, M. A. and R. J. Bull, "Induction of Strand Breaks in DNA by Trichloroethylene and Metabolites in Rat and Mouse Liver In Vivo," *Toxicology and Applied Pharmacology*, 94:45-54, 1988.
13. Russo, A., F. Pacchierotti, and P. Metalli, "Nondisjunction Induced in Mouse Spermatogenesis by Chloral Hydrate, a Metabolite of Trichloroethylene," *Environmental Mutagenesis*, 6:695-703, 1984.
14. "Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies)," National Toxicology Program Technical Report Series No. 243, NIH Publication No. 90-1799, 1990.
15. National Cancer Institute, "Carcinogenesis Bioassay of Trichloroethylene," CAS No. 97-01-6, D.H.E.W. Publication No. (NIH) 76-802, 1976.
16. Herren-Freund, S. L., et al., "The Carcinogenicity of Trichloroethylene and its Metabolites, Trichloroacetic Acid and Dichloroacetic Acid in Mouse Liver," *Toxicology and Applied Pharmacology*, 90:183-189, 1987.
17. National Cancer Institute, "Bioassay of Tetrachloroethylene for Possible Carcinogenicity," D.H.E.W. Publication No. 77-813, 1977.
18. Crebelli, R. and A. Carere, "Genetic Toxicology of 1,1,2,-Trichloroethylene," *Mutation Research*, 221:11-37, 1989.

FDA invites interested parties to submit relevant information, including ongoing toxicological studies, current or future trends in use patterns and human exposure levels, and toxicological data, to the agency. Interested persons may, on or before August 23, 1993, submit information to the Dockets Management Branch (address above). Two copies of any information are to be submitted, except that individuals may submit one copy. Submissions are to be identified with the docket number found in brackets in the heading of this document. Received submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: July 16, 1993.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 93-17498 Filed 7-22-93; 8:45 am]

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